Testimony of Peter R. Paradiso: Senate Special Committee on Aging: November 16, 2004

Introduction

Good Morning Mr. Chairman and members of the committee. My name is Peter Paradiso and I am the Vice President for New Business and Scientific Affairs at Wyeth. Wyeth has been in the business of researching and manufacturing vaccines and biological products for over 100 years and I have been part of that effort for the past 20 years. We are proud of the contributions we have made to public health throughout this time including our contribution to the eradication of smallpox worldwide not only through the supply of vaccine and the technology for a bifurcated needle delivery device critical to the mass immunization programs. For nearly 20 years we were also the sole U.S. producer of oral polio vaccine, which conquered polio disease in the U.S. with the last case of indigenous disease occurring in 1979.

Most recently we introduced the first conjugate vaccine to prevent meningitis and other invasive infections of childhood caused by the pneumococcal bacteria, an organism that not only causes serious diseases, but also was developing antibiotic resistance at an alarming rate. In the 4 years that this vaccine, named Prevnar, has been on the market in the U.S., childhood pneumococcal disease has declined by over 80 percent. Furthermore, studies have shown that invasive disease caused by pneumococcus in adults has also decreased significantly due to fewer ill children spreading disease to adults. In total this means that not only have serious diseases and death declined but the need to use antibiotics has decreased as well which should serve to stem the rising tide of antibiotic resistance. While I speak of Wyeth vaccines in particular, vaccines made by our competitors can boast of the same type of dramatic results in decreasing or in some cases eliminating the former scourges of childhood diseases. The record shows that vaccines have had one of, if not the greatest impact of any public health intervention over the last century.

As important as these products are to society, it has become increasingly difficult to justify remaining in the vaccine business. While the primary focus of this hearing is on influenza vaccine, the shortage of flu vaccine and flu vaccine manufacturers is but a symptom of a larger problem. There are only four companies left that make vaccines routinely used in childhood. Many vaccines are now made by only one company. And while it did not grab the public's attention to the extent of the flu vaccine shortage, during the early part

of this decade most children's vaccines experienced dramatic shortages as well. To address flu vaccine supply and the limited number of manufacturers, one must look at the small number of manufacturers overall, and understand the reasons that the current situation exists.

In February 2002, the National Vaccine Advisory Committee (NVAC), under the auspices of the National Vaccine Program Office (NVPO), reviewed the issues associated with the shortages in vaccine supplies. The conclusions of this detailed assessment highlighted numerous efforts that could impact vaccine supply in a positive way. These strategies included, among others, expansion of vaccine stockpiles, increased support for regulatory agencies, maintenance and strengthening of liability protections, financial incentives to manufacturers, streamlining the regulatory process without compromising safety or efficacy, and a campaign to emphasize the benefits of vaccination. I will highlight several of these issues in my comments but all of them are important and thoughtful approaches to the vaccine supply issue.

Every company must weigh the benefits versus the risks in each business opportunity when deciding where to place its resources. Some unappealing factors are inherent to vaccines and not to other types of drugs. As an example, most vaccines are used by children in a particular age group and for a defined and limited number of doses. This is in contrast, for example, to drugs for hypertension, which are taken by a significant portion of adults across multiple birth cohorts and are taken multiple times a day perhaps for the lifespan of the individual. Also as a society we are generally willing to pay more for products that treat diseases than for products that prevent them. One very telling figure that illustrates these points is that the total worldwide market for vaccines made by all manufacturers around the globe is estimated to be around $8 billion. There are single drugs on the market that rival the size of the global vaccine market.

Another inherent feature is that many drug products that are successful in the market find themselves with an ever-expanding market as new medical applications are found. With vaccines, the more effective a product is, the more likely it is to become obsolete. The smallpox and oral polio vaccines are both examples of highly effective products that worked themselves out of a market by eliminating disease.

I will address issues that relate to the changing environment in the vaccine field. These include changes in research and development, manufacturing, regulation,

liability and the overall marketplace dynamics. In addition, I will touch on some potential areas where this Congress can have a positive impact on securing vaccine supply.

Vaccine Research and Development

Some of the unattractive facets of the vaccine business are not inherent but are the result of government policies, some justifiable and others more questionable, that have an impact on the development process and can result in barriers that hinder existing vaccine research companies and serve as disincentives to new participants. These derive, in part, from a mindset intolerant of even theoretical risk and therefore often skew the risk/benefit ratio to the point where the benefit is forgotten. This intolerance for risk is reflected in some government policies.

Clinical trials for vaccines are much larger in scope than for drugs, which one would expect since these are products that are given to largely healthy individuals. The clinical trials for our Prevnar vaccine included over 40,000 children. Press reports about a vaccine to prevent childhood diarrhea under development at other companies have indicated that more than 60,000 children are in each trial. By contrast, drug trials typically involve 3000-5000 people. Importantly, however, vaccine development has become much more complex and costly over the last ten years. This ranges from increasingly stringent requirements for producing test vaccines to be used in clinical trials, to larger and more complex clinical programs. In fact, over the last five years in our company, the majority of the new hires in vaccines R&D are working in compliance, quality assurance or regulatory affairs rather than doing actual vaccine research. This has significantly increased our costs and lengthened our timelines.

Manufacturing

The complexity of manufacturing a vaccine is much higher than for small molecule drugs (e.g., pills) in part because of the use of living organisms as opposed to a more predictable chemical process and in part because of the subsequent complexity of the quality control and compliance processes. It takes approximately five years to build and validate a vaccines manufacturing facility. As a result, it is necessary to commit to building facilities at the same time that pivotal clinical trials are starting and while their outcome is uncertain.

However, the investments in manufacturing do not end with licensure. Using Prevnar as an example, this product is manufactured in two facilities that were licensed in 2000 after inspections by reviewers from the Centers for Biologics Evaluation and Review (CBER). Since then, to improve compliance and increase production capacity, we have made significant changes in these facilities and in our manufacturing and quality processes. Over $300M of capital has been invested in existing Prevnar facilities since 2000 and operating expenses have nearly doubled in the past three years. Over 2,000 people are involved in the manufacture of Prevnar and an additional 500 people are employed to insure that we are compliant with all of the regulatory requirements. It takes, on average, 50 weeks to produce and release a batch of product. It is, in part, this timeline that makes rapid response to shortages very difficult.

Once licensed, it is possible to rationalize this level of investment for a new product like Prevnar for which we are the sole global supplier. It is much more difficult to justify the ongoing investment for older products with prices reflective of the environment decades ago. This need to make significant investments in facilities to meet ever more stringent cGMP (good manufacturing practices) requirements becomes a critical factor in deciding whether to continue to keep a product on the market. In the case of Wyeth's DTaP and influenza vaccines, this continued investment could not be justified. Due to the vigilance of FDA and the efforts of manufacturers, the safety record of vaccine manufacturing and supply is exemplary.

The Vaccine Marketplace

Once on the market, pediatric vaccines, which constitute the bulk of vaccine products, must deal with the fact that roughly 60 percent of the U.S. market is one customer, the federal government. Having one customer with that degree of dominance in the market is daunting enough but when that customer has the legal power behind it to control prices, the market becomes much less attractive. Further, some states have ignored definitions in federal law and have taken steps that would make the percentage of the government market even greater. To date the Department of Health & Human Services (HHS) has not undertaken any activity to uphold federal law and inhibit that expansion.

When the Vaccines for Children program passed the Congress as part of OBRA '93, it created price controls on the vaccines that were on the market at that time. This situation has become so egregious that the price for tetanus vaccine is so low that no company has bid to provide it to the government for many years. Merck's MMR vaccine is listed on the government schedule at around $16.25 while the market catalog price is $38.05. Haemophilus influenzae type b vaccines are capped at $7.65/dose but are over $21.78/dose in the private market. The CDC is the largest purchaser among the government agencies, and has the leverage of a price controlled federal supply schedule, designed primarily for use by the VA and DOD, to use in driving prices downward. While it is an obligation of government to be a prudent purchaser, it is also an obligation of government to protect the public health. By over-emphasizing the former, one risks jeopardizing the latter.

Liability

One poorly understood risk of being in the vaccine business is liability. Since vaccines are so stringently regulated, both before and after marketing, and have such an outstanding record of safety, it might seem baffling why liability should be so problematic. The root of the problem lies in the fact that vaccines are given to virtually every young child in this country and as every parent knows, many diseases and afflictions manifest themselves in young children. The likelihood that any of these conditions would occur in temporal proximity to an immunization is high just because of the frequency with which shots are given.

Further, since nearly every child receives vaccines, any affliction without a known cause could be blamed on immunizations the child has received. Since the advent of the Internet, numerous unsubstantiated theories about vaccines have abounded. Over the course of the past 15 years, vaccines have been accused of causing epilepsy, multiple sclerosis, autism, attention deficit disorder, cancer, autoimmune disorders, learning disabilities, and Gulf War Syndrome. Vaccines have even been accused of being the cause of the AIDS epidemic. Today's allegations linking vaccines to autism are but the latest in a long history of accusations, none of which have been proven to have scientific validity.

While there were many more manufacturers making children's vaccines in the 1970's, that number has dwindled now to just four. The decrease has several causes but clearly the mostly precipitous decline occurred in the early 1980's as

manufacturers left the market due to an explosion of lawsuits alleging damage from DTP vaccine. This explosion of litigation scared liability insurers away from vaccines and companies were left with no insurance coverage. The situation became so perilous that there was only one company left making this vaccine, which prevents diphtheria, tetanus, and whooping cough, and public health officials had to take the step of not immunizing two year olds against these diseases because of vaccine shortages. The one remaining company was forced to raise its price to cover the cost of litigation and at the height of the problem fully 75 percent of the cost of DTP vaccine was directly attributable to the cost of litigation.

Congress intervened in 1986 and created the Vaccine Injury Compensation Program (VICP) administered by the Department of Health & Human Services to cover vaccines routinely recommended for use in children. This program was created to ease recovery for alleged vaccine-related injuries while protecting manufacturers from the costs and uncertainties of litigation that could potentially jeopardize the Nation's vaccine supply. There is a widespread perception that this program shields companies from liability but that is not the case. The law requires that anyone alleging an injury from a vaccine must first file a claim in the compensation program. However, whatever the decision from the program as to whether or not the injury was actually caused by a vaccine, the claimant has a right to leave the compensation program and proceed against the vaccine manufacturer in civil court. Furthermore, if a claim has been pending for more than 240 days and no decision has yet been rendered, a claimant can opt out of the program and proceed against the vaccine manufacturer in civil court.

The VICP determines the validity of claims based on the preponderance of the scientific evidence. A petitioner who has sustained an injury on the table of compensable events during the specified time period is presumed to have a vaccine related injury and is compensated by the VICP without having to actually demonstrate causation or fault. If a petitioner brings a claim for an injury that is not listed on the table, then the petitioner must show by the preponderance of the scientific evidence that the injury was caused by vaccine, but unlike civil court, the claimant does not have to demonstrate that the vaccine was defective. Since the inception of the program in 1986, the Institute of Medicine has done periodic reviews of scientific studies and has reached various conclusions related to causation which have in turn aided the VICP in determining causation.

Today, companies that make children's vaccines are facing a liability situation that dwarfs that of the 1980's when manufacturers were driven from the market. Each company has been served with over 350 lawsuits, some of them massive class actions, alleging injuries arising from the vaccine preservative thimerosal. There are also 4200 related pending petitions in the VICP, which are proceeding together as part of the Omnibus Autism Proceeding. These petitions, which may one day turn into lawsuits directed at manufacturers, allege that autism may be caused by MMR vaccination or the preservative thimerosal, formerly found in other childhood vaccines, or by some combination of the two.

In May 2004, the Institute of Medicine issued a report concluding that there is sufficient scientific evidence to reject a causal relationship between autism and vaccines. Although to date, not one of the 350 or so lawsuits has proceeded to trial, we estimate that the companies involved in this litigation have spent more than $200 million collectively in outside legal costs. Actual trials seeking damages for injuries are scheduled to commence early next year, at which point the legal costs will increase exponentially. Further, executives and scientists from the companies will spend countless hours in depositions and at trial. While there is overwhelming scientific evidence refuting any alleged link between vaccines and autism, no company would want the dynamics of a jury contemplating a disabled child versus a faceless corporation.

Recent Changes in the Wyeth Vaccine Business

All of the factors laid out above serve as the context in which our decision was made to leave various vaccine businesses including flu vaccine, and the routinely used DTaP vaccine for children. Regarding influenza, Wyeth had produced this vaccine in Marietta, PA, for nearly 20 years. A new manufacturing facility was built in the 1990s and licensed in 1998. We announced in November 2002 that the 2002-2003 would be our last season in the business. Our influenza vaccine business had lost money in four of its previous five years due largely to doses left unsold at the end of each season. Compounding that situation was the fact that in 2000, two years after licensure of the new manufacturing facility, the FDA informed us that extensive changes would need to be made at the site to remain in compliance with evolving standards. Wyeth reached an agreement with the FDA to enter into a consent decree focusing on the company's compliance with current Good Manufacturing Practices (cGMP). One of the sites involved was our flu manufacturing facility in Marietta, PA. When this significant compliance action was taken, FDA publicly acknowledged that there had been no safety

risk to patients with any products that had been made at that site. During the interval from 2000 to when we close the doors at the facility at the end of this year, we will have invested over $100 million in capital improvements for that facility alone. We could not justify further investment. If we had opted to persist in the flu vaccine business, many more millions of dollars in investment would have been required and our manufacturing costs would have continued to escalate.

Faced with this financial prospect and coupled with the fact that we had eight million unsold doses of vaccine at the end of 2002, which signaled that ample supply of vaccine was available from two other manufacturers, the only rational decision was to leave this flu vaccine business.

Our decision to leave the DTaP business had some common factors with the flu situation. The facility in Pearl River, NY where DTaP was produced was also subject to the consent decree we agreed to in 2000. We had known for several years that our DTaP had a limited lifespan in the market. Pediatricians and public health officials were understandably interested in combining some of the children's vaccines into one shot to reduce the number of injections given to babies. We had undertaken clinical trials to combine our Hemophilus influenzae type b (Hib) vaccine with DTaP, but our trials showed, as did the trials of other manufacturers, that combining these products resulted in a diminished immune response to the Hib component. Other potential vaccines that could be combined with DTaP were Hepatitis B and inactivated polio vaccines. Since we did not make either of those but our competitors did, we realized that our DTaP would not be a viable product much longer. In July 1999, the U.S. Public Health Service asked manufacturers to move away from using the thimerosal preservative in their vaccines. The U.S. Public Health Service and the American Academy of Pediatrics felt that removal of this preservative would be a means of maintaining parental confidence in vaccines while both organizations acknowledged that there was no scientific evidence to suggest any danger from the product. Our vaccine would have required a new manufacturing process, clinical trials, and re-licensure. These development requirements, coupled with the significant facility investments and the short projected lifespan of the product all contributed to our exit from this market.

Potential Solutions

These are examples of the types of decisions facing vaccine companies in terms of justifying remaining in this business relative to other investment opportunities. As mentioned, some of relatively unattractive components of the vaccine business are inherent. Others, however, can and should be addressed. Senators Bingaman and Smith have introduced a bill (S. 2272) that would remove the price caps on children's vaccines. It would also implement a technical change needed by the CDC in order to develop a stockpile of pediatric vaccines to utilize in the event of shortages. And it would transfer a category of needy children from an appropriated CDC account to an entitlement program which would not only benefit these children and the state public health departments that serve them but would also help manufacturers of new vaccines to know that government funds would be available to pay for the roughly 60% of the market controlled by the government.

Senators Craig and Bayh have introduced a bill (S. 2038) that would provide tax incentives for upgrading or building a new vaccine facility. This would help diminish the cost differential spread between drug and vaccine facilities and would be very helpful, particularly if constructed so that the tax credits could be carried forward. S. 2038 also offers a method of purchasing unsold doses of flu vaccine at the end of the season.

The FDA has announced a project, which they call "GMPs for the 21st Century." Part of this endeavor is an examination of cGMP's (current good manufacturing practices) to determine if they are the correct approach. I would urge the FDA to make review of vaccine cGMP's a priority. The safety bar on vaccines must remain high but if FDA changes the requirements for cGMP it should only do so because of some demonstrable threat to the safety of the final product, not because it is possible to conduct a process differently. And finally, the liability burden facing companies needs to be addressed. Senators Frist and Gregg made an attempt to do so last year and a new start needs to be made to ensure that manufacturers are not crippled from lawsuits born of unsubstantiated claims.

Conclusions

In closing I would like to say that as a research scientist, I am very excited about the future of vaccines. Over the past 20 years I have been privileged to

be a part of the development of a number of childhood vaccines such as HibTITER, Meningitec and Prevnar that have had a dramatic impact on the health of children here and around the world. Advances in technology allow us to contemplate vaccines today that were beyond our dreams just a decade ago. At Wyeth, for example, we are working not only on vaccines for unconquered infectious diseases but also for conditions like Alzheimer's disease. Unfortunately while the scientific frontier is very exciting, the business barriers can be daunting. This is particularly true of companies contemplating entering this marketplace anew or maintaining an aging product portfolio. Thus even though we have been in the vaccines business for many years, we have discontinued several vaccine products in the past five years and have closed a vaccine research facility in Rochester, New York and a manufacturing facility in Marietta, PA. We remain committed to continuing our work in vaccine development because we recognize the incredible public health potential of these products and we hope that recent events will serve as a reminder of the fragility of this enterprise.

So I thank the committee for giving us the opportunity today to present our views and would urge you to continue to pursue ways to improve the business environment and stabilize the vaccine industry.